EFFECT OF DONOR DEMOGRAPHICS ON TRANSFUSION RECIPIENT OUTCOMES

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ABSTRACT

Background and Significance

Over 21M units of blood are transfused every year, making blood transfusion one of the most common medical interventions in the US. It can be lifesaving, but like many medical interventions, it is not without risks. Thus, most of transfusion research has focused on making the process safer and more accessible.

Recent developments in stem cell science – where the transfusion of young blood was shown to reverse stem cell aging and improve physiological function in older mice and conversely, the transfusion of old blood was shown to accelerate stem cell aging and worsen physiological function in younger mice – raise important questions regarding the content of blood being transfused and its associated risks and/or benefits.

Research Question

Do blood donor demographics such as age and sex affect outcomes in adult transfusion recipients in the intensive care unit (ICU)?

Methods

This is a multi-center retrospective review examining the relationship between blood donor demographics such as age and sex and outcomes in adult ICU patients aged at least 18 years who received at least one unit (u) of packed red blood cells (pRBC) or plasma or platelets within the first 72 hours of admission. The outcomes of interest are: mortality rate, number of intensive care unit (ICU) days, and hospital length of stay (LOS) days. IRB approval was obtained from BHS on December 11, 2018.

Analysis was performed on the average donor age and the average donor sex (where male=1, female=0) against the specified patient outcome measures. Logistic regression was done to ascertain odds of mortality. Linear regression was done to ascertain prediction for ICU and LOS days.

Results

A total of 12,134 adult ICU patient records that corresponded to 65,003 blood donations were included in the analysis. There is no significant association between donor age and donor sex and mortality rate (p=0.74 and 0.59, respectively), number of ICU days (p=0.65 and 0.92, respectively), and hospital LOS (p=0.15 and 0.58, respectively).

Conclusions

The overall trend is that there is no association between donor age and sex with mortality, ICU days and hospital LOS in adult ICU patients. However, the study has a limited sample size and is underpowered (n=12,134 vs n=15,252). Conflicting findings among similar studies highlight the importance of taking into account the characteristics of both the donor and the recipient in the analysis.

Future prospects include determining the relationship between the recipient-donor age differential and patient outcomes. Subset analyses for each of the blood product types should be done since the number of units of specific blood product types impacts outcomes. Additionally, excluding outliers (i.e. extremely long ICU or hospital stays) may reveal small differences in outcomes (i.e. shortening ICU admission by 1 day).

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INTRODUCTION

Over 21M units of blood are transfused every year, making blood transfusion one of the most common medical interventions in the US.[1] It can be a lifesaving intervention, but it is not without risks. Like with most medical interventions, adverse reactions are well-documented. Fortunately, since the first successful whole blood transfusion in the 1960's, transfusion medicine has come a long way to make the process safer and more accessible.

Recent developments in stem cell science – where age-dependent factors circulating in the blood have been found to influence stem cell aging and physiological function in heterochronic parabiosis (HP) mouse models – raise important questions regarding the relationship between blood donor age and recipient outcomes.

In HP, two mice of different ages are stitched together at the skin such that their blood supplies are linked. Through the years, HP experiments have been shown to reverse stem cell aging in multiple tissue types.[2-6] These results were replicated by transfusing aged mice with plasma from young mice.[7] Furthermore, the injection of GDF-11, a circulating factor in the blood that is found in higher levels in young mice, has been shown to improve strength and endurance exercise capacity recovery from muscle injury[8] as well as to promote neurogenesis and improve olfactory discrimination in aging mice.[9] These studies provide evidence that factors circulating in the blood have the capability to modulate the function of stem cells and reverse the aging process.

The purpose of this retrospective study is to examine whether blood transfusions from younger donors yield mortality benefits in humans. Our hypothesis is that patients receiving blood from younger donors of the same sex have improved overall survival, and shorter hospital and ICU stays.

RESEARCH METHODS AND MATERIALS

Study Design and Outcomes

This is a multi-center retrospective review across 19 hospitals within the Banner Health System (BHS) examining the relationship between blood donor demographics such as age and sex and outcomes in adult ICU patients who received at least one unit (u) of packed red blood cells (pRBC) or plasma or platelets between January 1, 2003 and January 1, 2018. The outcomes of interest are: mortality rate, number of intensive care unit (ICU) days, and hospital length of stay (LOS) days. IRB approval was obtained from BHS on December 11, 2018.

Sample Population

Inclusion Criteria

The sample population consists of all adult (18 years and above) patients (also referred to as recipients) who were admitted to the ICU for at least part of their hospital admission and who received at least one unit of pRBC or plasma or platelets within the first 72 hours of their admission to any one of the following Banner Health Hospitals: Banner University Medical Center – Phoenix, Banner University Medical Center – Tucson, Banner Estrella Medical Center, Banner Gateway/ M.D. Anderson Medical Center, Banner Desert/ Cardon's Children's Medical Center, Banner Thunderbird Medical Center, Banner Boswell Medical Center, Banner Baywood Medical Center, Banner Ironwood Medical Center, Banner Del E Webb Medical Center, Banner Heart Hospital, Banner Goldfield Medical Center, Banner Casa Grande Medical Center, Banner Payson Medical Center, and Banner University Medical Center – South Campus. The transfused blood product must have been supplied by Vitalant.

Exclusion Criteria

The following were excluded from the study: patients with incorrect or incomplete records, and patients who received blood from donors with incorrect or incomplete records.

Data Collection

Data was obtained via the Honest Broker Clinical Research Data Warehouse (CRDW) of Banner University Medical Center Phoenix. Transfusion recipient data (age, sex, race, transfusion history, number of ICU days, and hospital LOS) was obtained from the Electronic Health Records and the Electronic Data Warehouse of BHS. The Donor Identification Number (DIN) for each transfusion was then used to obtain donor data (age, sex, donation date) from Vitalant. This was then merged with the transfusion recipient data and de-identified by honest broker staff for analysis.

Data Analysis

Analysis was performed on the average donor age and the average donor sex (where male=1, female=0) against the specified patient outcome measures. Logistic regression was done to ascertain odds of mortality. Linear regression was done to ascertain prediction for ICU and LOS days. All statistical analyses were done using STATA version 14 (STATAcorp; College Station, TX).

Power Calculation

If the difference in the proportion of mortality is 20%, 186 patients per year-increment (spanning from 18-100 years of age) are needed to render a statistical power of 80% with an alpha of 0.05; thus requiring at least 15,252 patients.

RESULTS

Sample Population

Over the study period, 24,544 ICU patients received at least one unit of blood (pRBC or plasma or platelets). Of these, 12,134 (49.4%) were adult ICU patients (18 years old and up) who received at least one unit of blood (pRBC or plasma or platelets) within the first 72 hours of admission. Of these, 56.24% were male and 43.76% were female. The mean patient age was 65.26 years (SD 16.35) (Table 1).

On average, each patient received 2.86u pRBC (SD 4.17), 1.88u plasma (SD 4.73), and 0.63u platelets (SD 1.65). The overall mortality rate was 15.21% (n=1,846) and the average number of days in the ICU and in the hospital were 3.33 (SD 11.21) and 8.88 (SD 7.97), respectively (Table 1).

Table 5. Characteristics and demographics of the patient and donor populations.

Variables	Value
Patient Demographics (n=12,134)	
Age, years (mean, SD)	65.26 (16.35)
Sex (male, %)	6,824 (56.24)
Donor Demographics (n=65,003)	
Age, years (mean, SD)	44.85 (12.25)
Sex (mean, SD)	0.65 (0.32)
Male, n (%)	42,481 (65.35)
Female, n (%)	22,522 (34.65)
Total Transfused Units per Patient	
pRBC, units (mean, SD)	2.86 (4.17)
Plasma, units (mean, SD)	1.88 (4.73)
Platelets, units (mean, SD)	0.63 (1.65)
Outcomes	
ICU days (mean, SD)	3.33 (11.21)
Length of Stay, days (mean, SD)	8.88 (7.97)
Mortality (yes, %)	1,846 (15.21)

Blood Donor Population

Over the study period, there was a total of 154,443 blood donations, 129,031 (83.55%) of which matched Vitalant records. For the analysis, 65,003 (42.09%) blood donations satisfied the inclusion criteria. The mean donor age was 44.85 years (SD 12.25) with 65.4% of donors being male and 34.6% female (Table 1).

Outcomes

Mortality

There is no significant association between donor age or sex and mortality rate (p=0.74 and 0.59, respectively). The following were found to increase the likelihood of mortality: recipient age (OR 1.01, p<0.001), pRBC units (OR 1.03, p<0.001), plasma units (OR 1.06, p<0.001), and platelet units (OR 1.03, p=0.04). Recipient gender had no association with mortality (OR 0.91, p=0.065) (Table 2).

Table 6. Factors associated with mortality risk.

Variables	OR (95% CI)	P-value
Recipient Age	1.01 (1.00, 1.01)	<0.001
Recipient Gender	0.91 (0.82, 1.01)	0.065
Average Donor Age	1.00 (0.99, 1.00)	0.748
Average Donor Gender	1.05 (0.89, 1.23)	0.596
Total Plasma	1.06 (1.05, 1.08)	<0.001
Total Platelets	1.03 (1.00, 1.07)	0.040
Total RBC	1.03 (1.02, 1.05)	<0.001

Since increasing patient age and length of stay in the ICU or the hospital are typically associated with increased mortality, we also examined the relationship of these variables with mortality. There was a significant difference in the patient age and hospital LOS between patients who survived and expired ($p=0.03$ and <0.001, respectively). There was no significant difference in the number of ICU days between patients who survived and expired ($p=0.18$) (Figure 1).

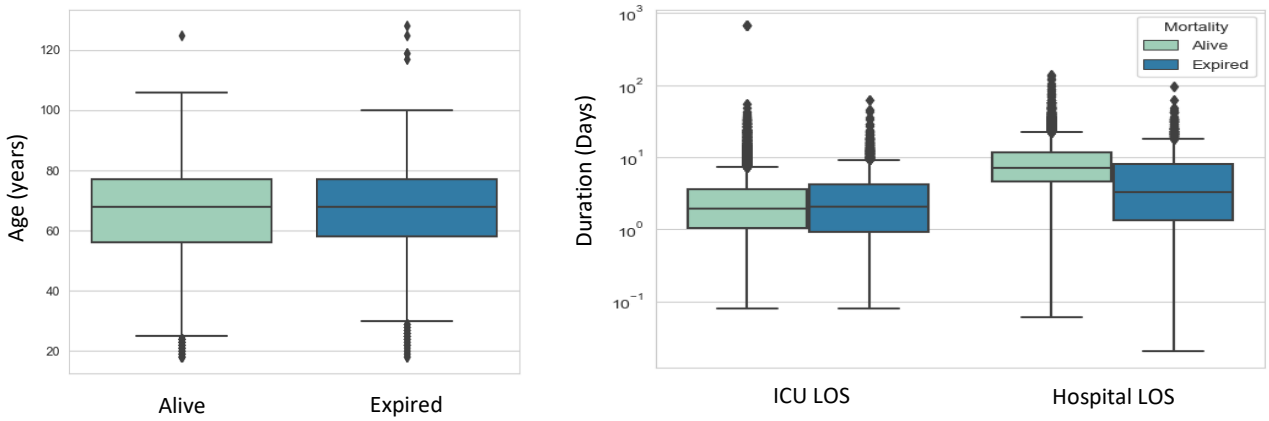

Figure 3. Comparison of mortality groups based on patient age (left), and ICU and hospital length of stay (right). Legend: Line- median; box- second and third quartiles; lower whisker to bottom box border- first quartile; bottom box border to line- second quartile; line to upper box border- third quartile; upper box border to upper whisker- fourth quartile; diamonds- outliers.

ICU Length of Stay

There is no significant association between donor age or sex and length of ICU stay (β 0.004, p=0.65; and β 0.034, p=0.92, respectively). The following were found to be associated with more ICU days: pRBC units (β 0.15, p<0.001), and platelet units (β 0.24, p=0.001). Recipient age and gender were not associated with ICU length of stay (β-0.003, p=0.59; and β=0.237, p=0.25, respectively) (Table 3).

Outcome	Variable	Beta (95% CI)	p-value
ICU LOS	Recipient Age	-0.003 (-0.02, 0.009)	0.595
	Recipient Gender	0.237 (-0.16, 0.64)	0.249
	Average Donor Age	0.004 (-0.013, 0.02)	0.652
	Average Donor Gender	0.034 (-0.60, 0.66)	0.922
	Total Plasma	0.034 (-0.01, 0.08)	0.172
	Total Platelets	0.242 (0.10, 0.38)	0.001
	Total RBC	0.147 (0.09, 0.21)	<0.001

Table 7. Factors associated with ICU length of stay.

Hospital Length of Stay

There is no significant association between donor age or sex and hospital LOS (β -0.008, p=0.15; and β 0.122, p=0.58, respectively). The following were found to be associated with a longer hospital LOS: recipient age (β -0.016, p<0.001), pRBC units (β 0.29, p<0.001), plasma units (β 0.06, p=0.001), and platelet units (β 0.39, p<0.001). Recipient gender was not associated with hospital LOS (β 0.264, p=0.064) (Table 4).

Outcome	Variable	Beta (95% CI)	p-value
Hospital LOS	Recipient Age	-0.016 (-0.02, -0.007)	<0.001
	Recipient Gender	0.264 (-0.02, -0.54)	0.064
	Average Donor Age	-0.008 (-0.02, 0.003)	0.145
	Average Donor Gender	0.122 (-0.31, 0.56)	0.581
	Total Plasma	0.056 (0.02, 0.09)	0.001
	Total Platelets	0.391 (0.29, 0.49)	<0.001
	Total RBC	0.294 (0.25, 0.34)	<0.001

Table 8. Factors associated with hospital length of stay.

DISCUSSION

Sample Population

In this initial analysis, there were 10 patients whose ages were above 100 years with a maximum value of 128 years. According to the 2010 US Census Report, there are approximately 1.73 centenarians per 10,000 in the US.[10] While it is possible that some of the patients in the sample are centenarians –it is more likely that these are either clerical errors or unknown values and should be excluded in future analyses.

Donor Population

In terms of age distribution, the donor population of the study closely resembles the national donor population except for an increased proportion of donors over 65 years of age (Figure 2). This means that if there were any risks associated with older donors, this study would magnify those effects. There is no published data on the sex distribution of blood donors in the US.

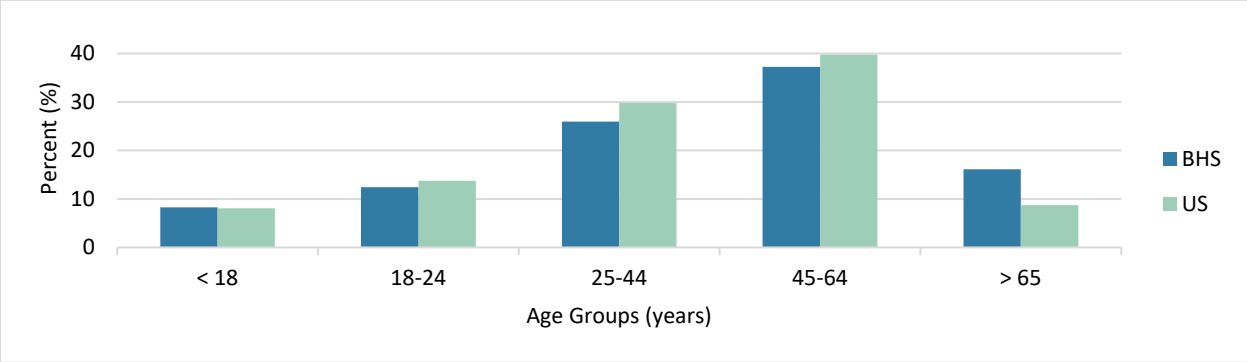

Figure 4. Comparison of blood donor age distribution at the Banner Health System (2003-2018) versus US statistics by the World Health Organization (2008).[11]

Study Outcomes

Donor Age and Outcomes

There is no association between donor age with mortality, ICU LOS and hospital LOS in adult ICU patients. A few retrospective studies investigating the relationship between donor age and recipient outcomes have had similar results.

The first study used national data on pRBC and plasma transfusion recipients (n=45,664 and n=136,639, respectively) from the Scandinavian Donations and Transfusions Database (SCANDAT2) and found no association between donor age (ie, as <25, 25-50, >50 years) and 30-day and 1-year mortality.[1] However, the analysis only considered the first 7 days of transfusions which discounts all other exposures. Following this, a study out of Duke University found no association between pRBC donor age (ie, as 17-37, 38-50, 51-86 years) and patient mortality, LOS and acute kidney injury (AKI) rates in patients receiving plasma perioperatively for coronary artery bypass grafting surgery (n=1,306).[2]

The discordance of these results with mouse studies has been attributed to inadequate exposure in terms of dose and duration. In HP, half of the older mouse's blood supply is from the young mouse, while the median number of units transfused were 2.86, 1.88, and 0.63 for pRBC, plasma and platelets, respectively for an estimated total volume of 1.7L. This roughly corresponds to about 34% of the 5-liter total blood supply of an average sized man (70kg). Furthermore, transfused blood products typically have a shorter effective lifespan than native blood due to biochemical changes during storage.[12]

However, a Canadian retrospective study (n=30,503) looking at cumulative pRBC transfusions over time did show an increased risk of death with younger donors compared to donors in the 40-49.9-year old range (adjusted hazard ratio (AHR) 1.08, p <0.001 for age range 17-19.9 years; and AHR 1.06, p<0.001 for age range 20-29.9 years).[3] These findings contradict those from mouse models[4] and have been attributed to the healthy donor phenomenon.[5] This is a well-documented phenomenon in transfusion literature and is due to the fact that older individuals that are eligible to donate blood are generally healthier and have had more

encounters with the healthcare system whereas younger individuals may simply be asymptomatic from undiagnosed medical conditions.

Following this, a study using the methodology of the Canadian study on SCANDAT2 data (n=968,264) showed no association between donor age and sex with survival in patients receiving pRBC tranfusions.[6] Differences in patient population may account for the conflicting results (i.e., median recipient age 73 versus 69 years for the Scandinavian and the Canadian studies, respectively).

Donor Sex and Outcomes

While our study did not show any association between donor sex and patient outcomes, the evidence behind the role of female donor plasma in the development of transfusion-related acute lung injury (TRALI), the leading cause of transfusion-related mortality, has grown in recent years.

A large prospective, case-controlled study of TRALI showed decreased TRALI rates after reduction of transfusion of plasma from female donors.[13] This was attributed to the transfusion of reduced amounts of cognate HLA class II antibodies[14] and HNA antibodies[15] which have been shown to increase the risk of TRALI. These leukocyte antibodies are formed after exposure to their respective antigens through prior pregnancy, transfusion, or transplantation. Multiparous women, specifically, have been found to undergo anti-HLA and anti-HNA alloimmunization at higher frequencies.[16] Transfusion and transplant recipients are typically not eligible for blood donation[17] and thus would not affect transfusion outcomes.

Other Factors and Outcomes

Perhaps the association of recipient age and number of units transfused with mortality, ICU days and hospital LOS are due to overall health status as well as the indication for the transfusion and its severity.

Limitations

Because of the retrospective design of our study, our data is limited to what has been documented by BHS and Vitalant staff. It is possible that we may have missed mortalities because the patient expired outside of their admission and had no further encounters within

BHS. There is also a significant amount of records that had to be excluded due to incomplete or incorrect data points within the BHS electronic health record (EHR) and the Vitalant database.

This initial analysis was done in a broad population of adult ICU patients with numerous potential confounding factors such as nature and severity of primary disease, comorbidities, and indication for transfusion and no control group. Additionally, outliers were included in the analysis (ie, extremely high recipient age, and long hospital and ICU stays) which may have masked smaller effects on outcomes (ie, shortening ICU admission by 1 day).

It is possible that our study was underpowered (n=12,134 versus n=15,252 based on power calculation; however, any clinical relevance should have been uncovered in the second SCANDAT2 study given its sample size of 968,264.

FUTURE DIRECTIONS

The discrepancies between our findings and those of the Canadian and Scandinavian studies highlight the importance of taking into account the characteristics of both the donor and the recipient in the analysis. Future prospects include determining the relationship between the recipient:donor age differential and/or recipient:donor sex dyad (ie, M:M, M:F, F:F, and F:M) and patient outcomes.

Subset analyses for each of the blood product types should be done since the number of units of specific blood product types impacts outcomes. Additionally, excluding outliers (i.e. extremely long ICU or hospital stays) may reveal small differences in outcomes (i.e. shortening ICU admission by 1 day).

Since both mortality and length of stay are influenced by many factors, sometimes including hospital logistics, the lack of association between donor demographics and patient mortality and length of stay does not preclude the possibility of an association with more fine-grained outcomes such as rates of transfusion reactions, acute kidney injury (AKI), myocardial infarction (MI), ventilator- and hospital- associated pneumonias (VAP and HAP), central line-associated bloodstream infections (CLABSI), and catheter-associated urinary tract infections (CAUTI). Further analyses using these outcome measures might reveal differences between blood obtained from younger versus older donors.

CONCLUSIONS

There is no association between donor age and sex with mortality, ICU days and hospital LOS in adult ICU patients. However, the study has a limited sample size and is underpowered (n=12,134 vs n=15,252). Conflicting findings among similar studies highlight the importance of taking into account the characteristics of both the donor and the recipient in the analysis.

Future prospects include determining the relationship between the recipient-donor age differential and patient outcomes (including more fine-grained outcomes such as rates of transfusion reactions, AKI, MI, HAP/VAP, CAUTI, CLABSI, etc). Subset analyses for each of the blood product types should be done since the number of units of specific blood product types impacts outcomes. Subset analyses on specific adult ICU populations should also be done to minimize confounding factors. Additionally, excluding outliers (i.e. extremely long ICU or hospital stays) may reveal small differences in outcomes (i.e. shortening ICU admission by 1 day).

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